REMARKS

Claims 1-20 are pending in this application. Claims 1-7 are withdrawn as to a non-elected invention and claims 8-20 are under consideration.

Rejection under 35 USC § 112

Applicant notes that the rejection under 35 USC § 112 is no longer stated against the claims.

Rejections under 35 USC § 103

Claims 8-16 and 20 stand rejected over Builder *et al.*, US 4,620,948 in view of Valenzuela *et al.*, 1979. Nature 280:815-819. Applicant respectfully traverses.

Initially, Applicant must address the Examiner's misconception about Applicant's previous discussion of Builder. The Examiner stated "Applicant also argues that Builder et al., do not use the technique to purify HBsAg." (Action at page 3, lines 2-3). Applicant did make that statement. And Applicant does not argue that the method of Builder *et* al., is limited to any particular proteins. However, Applicant also described for the Examiner that Builder, *et al.*, teaches a method designed, in Builder's own words quoted below, for refolding insoluble proteins produced as refractile bodies. To wit, Builder *et al.*, states:

"A large number of human, mammalian, and other proteins, including, for example, human growth hormone, (hGH) bovine growth hormone (bGH) and a number of interferons have been produced in host cells by transfecting such cells with DNA encoding these proteins and growing resulting cells under conditions favorable to the expression of the new heterologous protein. Viral coat proteins, such as capsid proteins of foot and mouth disease (FMD) virus and the surface antigenic protein of hepatitis B virus (HBsAg) are still other examples of heterologous proteins which have also been produced in suitable recombinant DNA engineered hosts. The **heterologous protein is frequently precipitated** inside the cell, and constitutes a significant portion of the total cell protein." (lines 18-32, **emphasis** added).

Further, Builder *et al.*, contend:

"Various heterologous proteins expressed in bacterial host cells, for example, pGH, hGH, and viral coat proteins such as a fusion protein with FMD virus, protein and HBsAg form refractile bodies **to a greater or lesser extent** under commonly found culture conditions. Certain other

proteins such as immune interferon (IIF) and leukocyte interferon (LeIF) are more soluble in the cytoplasm. (Fibroblast interferon (FIF) is, however, refractile in host culture.)" (col. 6, lines 48-56, **emphasis** added)

Finally, Builder *et al.*, states:

"The invention herein is directed to procedures which are useful in isolating, purifying, and, if necessary, reactivating proteins which appear in host cells in the form of "refractile bodies". Part of the invention concerns methods which encourage such refractile body formation; **however, the procedures for protein recovery and activation disclosed herein are intended to be specifically applicable to such refractile proteins.**" (col 6, lines 30-37, **emphasis** added)

Builder *et al.*, teaches in both Scheme 1 (col 9-10) and Scheme 2 (Col 18), that in applying the method of their invention, processing the insoluble proteins found in refractile bodies includes steps to centrifuge the cell lysate and discard the supernatant. Applicant cited, in direct and opposite contrast, the method of Wampler *et al.*, which requires centrifugation and collection of supernatant. Any insoluble protein that may be produced, according to Builder *et al.*, "to a greater or lesser extent," is discarded in Wampler *et al.*, type processes. Therefore, the teaching of Builder *et al.*, is relevant to the refolding of insoluble proteins and "specifically applicable to refractile proteins." The reference is simply not relevant to processes involving soluble proteins.

In view of the above, previously incorporated into Applicant's remarks on the non-obviousness of the present invention, Applicant believes that the Examiner has simply not responded to, or perhaps misunderstood, Applicant's remarks of record. Moreover, rather than address the teaching of Wampler *et al.*, a reference believed to be relevant to the present claims as a prior art method of making soluble HBsAg, and a reference that attempted the use of a redox buffer, the Examiner chooses simply not to cite that reference. Instead, the Examiner cites Valenzuela *et al.* – a reference that provides only motivation to obtain properly folded HBsAg..

Wampler *et al.*, was discussed because the reference noted the use of a mixture of oxidized and reduced glutathione to refold proteins (page 6833, col 2, lines 42-55). Wampler *et al.*, concluded that method did not work to increase disulfide crosslinking in HBsAg and stated that their "results favor an oxidative mechanism for the thiocyanate conversion." (*Id*). The reference, like Valenzuela, notes the importance of correct disulfide formation in making recombinant HBsAg. However, unlike Valenzuela *et al.*, Wampler *et al.*, explicitly teaches away from the present invention.

A determination of whether claims are obvious or nonobvious is a consideration of many factors. Included in such a consideration is whether the prior art teaches away from the presently claimed invention. Applicant has brought the Wampler reference to the attention of the Examiner and considers the Examiner's refusal to address the teaching of Wampler *et al.*, unresponsive to Applicant's remarks and short circuiting the required analysis under § 103.

Valenzuela *et al.*, is seen to provide only motivation to achieve proper folding of recombinant HBsAg. The reference, being from the same field of HBsAg as Wampler *et al.*, is not seen to provide any motivation to go against the teaching of Wampler *et al.* Therefore, the reference does not make up for the deficiencies of Builder *et al.*, and does not contradict Wampler *et al.*

Therefore, Builder *et al.*, is not seen to be relevant in that it teaches a method of dissolving insoluble proteins, Valenzuela *et al.*, provides only general motivation and the Examiner has refused to consider relevant prior art, Applicant believes that the Examiner has not stated a proper case for the *prima facie* obviousness of the present claims.

Claims 17 – 19 were rejected over Builder *et al.* and Valenzuela *et al.*, in view of Petre *et al.*, or Even-Chen. Because neither Petre *et al.*, or Even-Chen make up for the deficiency of Builder *et al.* and Valenzuela *et al.*, as the primary references, the combinations can not provide the basis for a *prima facie* case of obviousness against the patentability of the present claims. Therefore, Applicant respectfully requests that all of the stated rejections against Claims 17-19 be withdrawn.

CONDITIONAL PETITION

Applicant hereby makes a Conditional Petition for any relief available to correct any defect in connection with this filing, or any defect remaining in this application after this filing. The Commissioner is authorized to charge deposit account 13-2755 for the petition fee and any other fee(s) required to effect this Conditional Petition.

CONCLUSION

Claims 8-20 are now believed to be presented in condition for Allowance. An early indication of the same is requested. The Examiner is invited to contact Applicant's Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

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